Contrast-Based Ultrasonic Blood Flow Measurements Based on Inflow/Outflow Time Intensities

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Abstract- **Ultrasonic contrast specific blood flow measurement techniques offer new opportunities to assess blood flow information based on evaluation of time-intensity curves (TICs). Such curves are measured to estimate concentration of the microbubbles in the blood pool. Based on the indicator-dilution theory, hemodynamic parameters such as the volume flow rate can be directly related to the time constant estimated from the TICs. In this paper, the applicability of the indicator-dilution theory is studied with an *in vitro* experiment setup. Moreover, the linear system assumption of the blood mixing mechanism is also tested. Several flow phantoms are constructed and a self-made, albumin based contrast agent is used. The TIC is measured by using B-mode images obtained from a commercial ultrasound system. It is found that with a bolus injection and a single mixing chamber, the estimated time constants agree with the theory despite that the effective mixing volume may be smaller than the actual mixing chamber volume in some conditions. More importantly, discrepancy also exists with a prolonged injection and/or two mixing chambers with cascade connection. In other words, the linear system assumption is still questionable even under the controlled *in vitro* experimental conditions. Potential sources of the discrepancy require further investigation in order to develop contrast specific quantitative blood flow measurement techniques.**

Keywords **- ultrasounic contrast agent, time-intensity curve**

I. Introduction

Recent studies have found the possibility of using contrast ultrasonography to assess *in vivo* flow information based on the time-intensity curve obtained from gray-scale images [1]-[2]. However, only **qualitative** analysis is possible to date, thus limiting clinical applications of ultrasonic contrast agents. Therefore, new approaches for **quantitative** flow measurements need to be developed. Some researches have been proposed to determine blood flow information based on the indicator dilution theory [3]-[4]. Both *in vitro* and *in vivo* experiments have been conducted. A fundamental assumption is that a quasilinear relation between ultrasonic echo intensity and the concentration of the microbubbles [4].

Traditional indicator dilution theory focuses on TIC at the output of the mixing chamber and estimates flow parameters when inflow can be viewed as an impulse function [5]. One problem associated with an intravenous injection is that the intensity is delayed and prolonged before reaching the mixing chamber. In other words, flow estimation of mixing chamber will be affected by the inflow conditions. In order to correct the influence of inflow of the mixing chamber, inflow/outflow TICs must be taken into account simultaneously in this situation.

The purpose of this study is to construct an *in vitro* flow experiment system and to investigate if the indicator dilution theory is useful for bolus and prolonged injection using gray-scale images.

II. Materials and Methods

A. Basic Principles

Assuming a certain amount of indicator solution is injected instantaneously into the system input and its concentration *c(t)* is monitored continuously at the output, the mean time of transit of the mixing chamber may be determined using the following expression:

$$MTT = \frac{\int_0^\alpha tc(t)dt}{\int_0^\alpha c(t)dt} \quad (1)$$

where *c(t)* is the measured concentration as a function of time *t*. MTT represents the time for the entire fluid volume to pass though the chamber, and it is inversely proportional to the flow rate.

The echo intensity measured at the output $I_o(t)$ of mixing chamber depends on the configuration of inflow $I_I(t)$. In other words, a prolonged injection will produce essentially different echo intensity at the outflow than that generated by a bolus injection. This difficulty may be resolved by using the deconvolution approach, assuming the mixing can be viewed as a linear system.

$$I_O(t) = I_I(t) \otimes h(t) \quad (2)$$

where $\otimes$ stands for convolution, and *h(t)* is the transfer function of the mixing chamber. Based on (2), output mean transit t_{out} equals the sum of the mixing chamber mean transit time t_{mix} plus the mean input transit time t_{in} [6], i.e.,

$$t_{mix} = t_{out} - t_{in} \quad (3)$$

In practice, contrast injections are not instantaneous. If we can find the mean injection time, then we can correctly to estimate the mixing chamber mean transit time.

B. Experimental Setup

There were two different approaches to measure the mean transit time of mixing chamber. The first one was to measure the output TIC of the mixing chamber only where input injection was given by a pulse, i.e. a bolus injection

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Abstract

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of the contrast agent. In our system, inflow/outflow time intensity curves were obtained simultaneously by a commercial ultrasound machine ATL Ultramark 9 (Advanced Technology Laboratories Inc., Wash., USA) with a 7MHz linear array transducer. Schematic diagrams of the data acquisition systems is shown in Fig. 2.

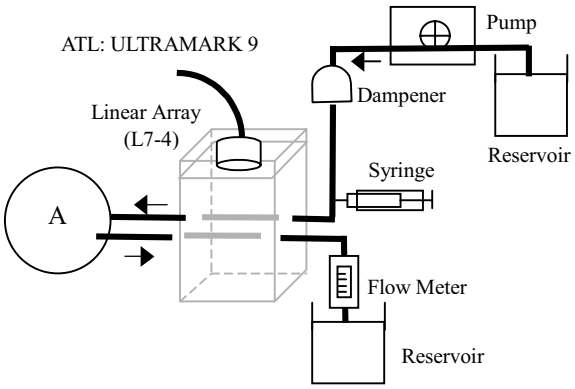


Fig. 2: Schematic diagrams of experiment I.

Two silicon tubes were placed in parallel with opposite flow direction. The diameter of the tubes was 0.8cm (34 pixels). Transducer was placed above the tubing and images were acquired one frame per second with a dynamic range of 50dB. With every bolus injection and different flow-rate setting, 300 digitized gray-scale frames were stored in a continuous loop and saved on a disk for later off-line analysis. To prevent recirculation of the contrast agent back in the phantom, the water in the system only passed the model once, so we could generate primary time-intensity curves. The image consisted of two regions of interest (ROIs). One was from the input vessel of the mixing chamber and the other was from the output vessel (as shown in Fig. 3). The image data were also converted from the logarithmic scale back to the linear scale before the time constants were calculated. We also used a circle with a diameter 34 pixels to search the position of tubing inner diameter and then summed the echo intensity inside the ROI for each image. The result was used as the intensity at that particular time instant.

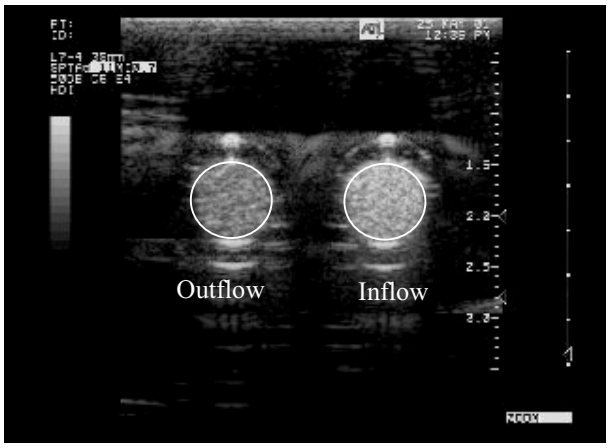


Fig. 3: Brightness mode image with two ROIs

The second group of experiments was to measure TICs using prolonged injection. Here, we used another hollow ball (200mL, chamber B) connected at the front side of mixing chamber (chamber A, 260mL). Bolus injection site was located at input end of new hollow ball B and thus the input injection of the mixing chamber was prolonged. Other conditions were the same with previous experiment setup. Experiment setup is shown in Fig. 4.

C. Self-made Constant Agent

The self-made contrast agent was made from albumin and based on the hand agitation technique. The self-made contrast agent comprised of 4mL of water, 1mL of 20% human albumin solution and 0.5mL air. The two syringes were then pushed in turns with the valve of the three-way stopcock closed at the needle site. After several pushings, a layer of foam was formed on the surface of the solution. The fluid below the layer of foam was used as the ultrasonic contrast agent. The size of the self-made microbubbles was estimated using a light microscope (EMZ-TR, MEIJI Tech. Co., Tokyo, Japan). The diameter ranged from 20μm to 50μm. To improve robustness of the TIC measurements, the measured intensity is fitted to a gamma function $g(t)$. The gamma function with the following form is employed

$$g(t) = \alpha (t - t_o)^r e^{-\beta (t - t_o)} \qquad (4)$$

where α and β are scaling factors and γ represents the skewness [7]. The MTT was calculated after gamma function fitting. Typical inflow/outflow unfitted and fitted TICs were shown in Fig. 5.

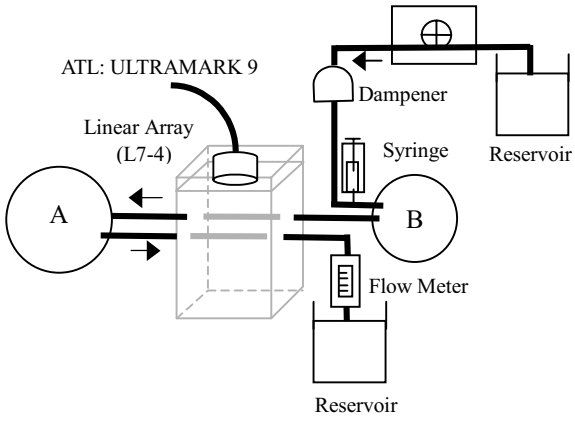


Fig. 4: Schematic diagrams of experiment II.

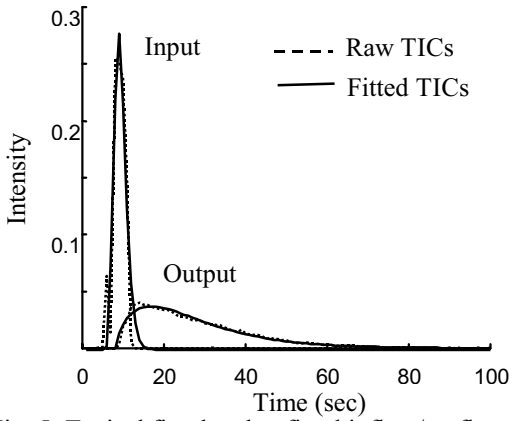


Fig. 5: Typical fitted and unfitted inflow/outflow TICs

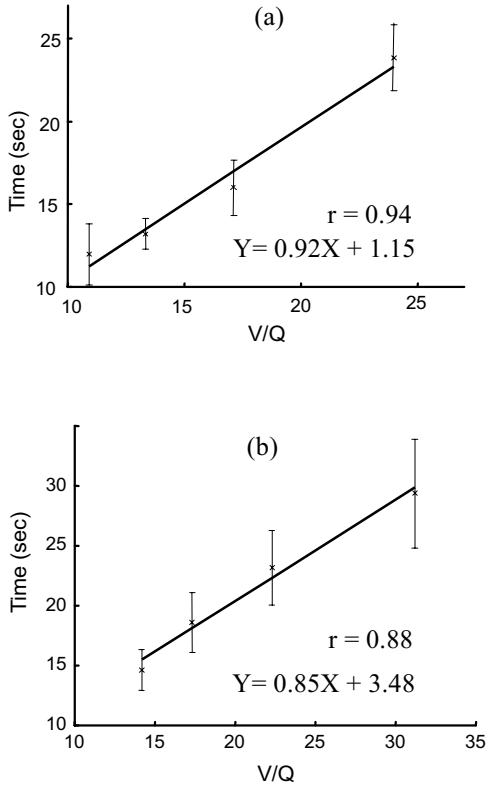
Ⅲ. RESULTS

In all results, the volume flow rates were 0.5, 0.7, 0.9 and 1.1L/min. For each case, 5 independent measurements were performed to obtain the average values and standard deviations.

A. Bolus Injection

In Figs. 6 (a) to (c), mixing chamber were 200, 260, 580mL, respectively and 5mL self-made contrast agent was injected continuously about 2 to 3 seconds. The horizontal axis represents the theoretical values (i.e., mixing chamber volume divided by flow rate). The vertical axis demonstrated the estimates of mean transit time from experimental output TIC after gamma function fitting.

From the results using linear regression method demonstrated that there were linear correlations (slope approached to 1) between theoretical values and estimate mean transit time of 200 and 260mL mixing chamber by a bolus injection. However, the results of 580mL mixing chamber were not in good agreement. It maybe due to that the bubbles into the larger mixing chamber did not dilute completely and left the mixing chamber. In other words, the indicator dilution theory may not be applicable and the effective volume for dilution is smaller in this case.



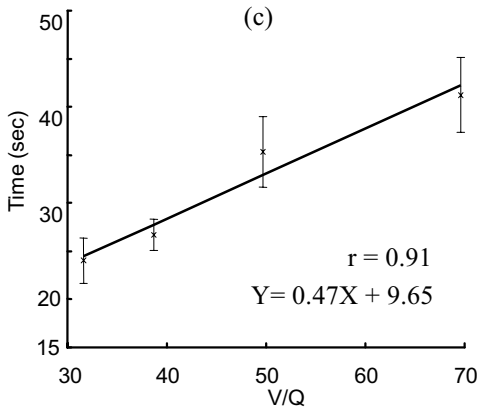


Fig. 6: Results of bolus injections for (a) 200, (b) 260 and (c) 580mL three mixing chambers

B. Prolonged Injection

Fig. 7 showed the results of prolonged injections. The output MTT of mixing chamber at different flow rates (dashed) was larger than the indicator dilution theoretical value (solid) possibly due to the prolonged injection. From (3), MTT of mixing chamber (dot-dashed) could be obtained by subtracting output MTT from input MTT (dotted). Results showed that the MTT of the mixing chamber was not close to the theoretical value. The input MTT was close to the hollow ball (200mL) at mixing chamber input side. Possible reasons include the tubing between the two hollow balls, the number of bubbles was reduced during the duration of experiments and the bubble concentration in prolonged injections was smaller than that in bolus injection.

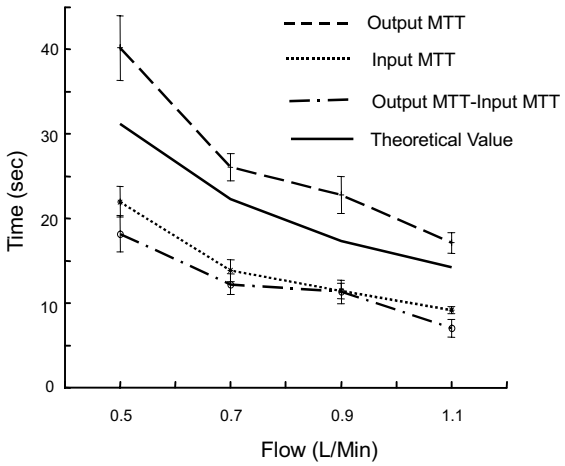


Fig. 6: Results for prolonged injection for a 260mL mixing chamber

Ⅳ. DISCUSSIONS and CONCLUSIONS

Correlation between the time-intensity curve and flow parameters were studied. In addition, we also extended by measuring acoustic intensity from both the vessel entering and the vessel leaving a mixing chamber. Experimental results of flow parameters obtained by bolus and prolonged injections were discussed. It is shown that our experiment system could offer an *in vitro* model to illustrate indicator dilution theory using ultrasonic contrast agent. Future work

will focus on estimation using various deconvolution techniques.

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